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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Linda O. Palladino
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

[REDACTED]
EXAMINER

TON, THAIAN N

ART UNIT	PAPER NUMBER
	1632

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,840	MURPHY ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 27 July 2004.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 51-78 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 51-78 is/are rejected.
- 7) Claim(s) 62, 74, 78 is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 15 February 2002 is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ . | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

The Examiner of Record is now Thaian N. Ton of Art Unit 1632.

Applicants' Amendment, filed 7/24/04, has been entered. Claims 1-50 have been cancelled. Claims 51-78 have been added. Claims 51-78 are pending. Claims 51-78 are under current examination.

Information Disclosure Statement

Applicants' IDS, filed 4/19/04 and 6/25/02, have been considered.

Election/Restrictions

Applicant's election of Group I in the reply filed on 7/27/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants state the following: [T]he examiner has kindly agreed to consider a claim to compositions made by the elected method." See p. 7, 2nd paragraph of the Response. Upon careful review of the record, it is noted that in the interview summary, mailed 7/19/04, the prior Examiner stated, "Examiner agreed that claims from claims from Group II could be redrafted to encompass method steps to generate a transgenic animal with the cells made with the method in Group I." *[Emphasis added]*. The newly added claims 62, 74 and 78 are directed to products,

in particular transgenic mice. They are not drafted as method steps to generate a transgenic animal using the claimed cells. However, it is ascertained that because no burden would be associated with examination of these claims, they will be examined with the claims of Group I.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See p. 38, line 13.

Claim Objections

Claims 62, 74 and 78 are objected to for the following: the claims recite a “transgenic non-human” mouse. Clearly, a mouse is not human. Cancellation of the term “non-human” would be remedial.

Claim 76 is objected to because of the following informalities: the claim recites the method of claim 74. Claim 74 is not a method claim. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent

the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 51-78 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,586,251 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods of genetically modifying an endogenous gene or chromosomal locus of interest. In particular, the '254 claims recite methods for genetically modifying an endogenous gene or chromosomal locus of interest using bacterial homologous recombination, which is obvious over the instant claims, which recite methods of creating a modified gene locus by site specific recombination. Thus, the '254 make obvious the instant claims.

Claims 51-78 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,596,541 B2. Although the conflicting claims are not identical, they are

not patentably distinct from each other because the instantly claimed methods and the '541 methods are both directed to creating a modified gene endogenous gene locus by site-specific recombination. In particular, the instant claims differ only with respect to replacing the immunoglobulin variable region locus (in the '541 claims), which is encompassed by the endogenous genes and chromosomal loci claimed in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mouse embryonic stem [ES] cells comprising a modified endogenous gene locus flanked by site-specific recombination sites, the specification does not reasonably provide enablement for ES cells comprising a modified endogenous gene locus flanked by site-specific recombination sites, for the breadth claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or us the invention commensurate in scope with these claims.

The specification teaches methods for engineering and utilizing large DNA vectors to target and modify, via homologous recombination, endogenous genes and chromosomal loci in eukaryotic cells. Further, the specification teaches that the described method is used to engineer genetically modified eukaryotic cells [in particular, mammalian ES cells], which would be used to generate non-human organisms. The specification describes preferred embodiments of the claimed invention, particularly methods of producing non-human organisms containing the genetically modified endogenous gene or chromosomal locus produced by the claimed method.

The breadth of the claimed invention encompasses the use of ES cells from any species. However, the state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only “putative” ES cells exist for other species (see Moreadith *et al.*, *J. Mol. Med.*, 1997, p. 214, *Summary*). Note that “putative” ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith *et al.* supports this observation as they discuss the historical perspective of mouse ES cells as follows:

“The stage was set—one could grow normal, diploid ES cells in culture for multiple passages without loss of the ability to contribute to normal development. Furthermore, the cells contributed to the development of gametes at a high frequency (germline competence) and the haploid genomes of these cells were transmitted to the next generation. Thus, the introduction of mutations in these cells offered the possibility of producing mice with a predetermined genotype.”

Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of any species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal.

In addition, prior to the time of filing, Mullins *et al.* (*Journal of Clinical Investigation*, 1996) report that “although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated.” (page 1558, column 2, first paragraph). As the claims are encompass methods involving the manipulation of embryonic stem (ES), and particularly since the subject matter of the specification and the claimed invention encompasses the use of such cells for the generation of animals, the state of the art supports that only mouse ES cells were available for use to produce the claimed transgenic mice.

The instant specification fails to provide any teachings or guidance with regard to the generation of a transgenic mouse which is capable of expression of chimeric or human antibodies, as presently claimed. The instant specification teaches that the production of various antigens in non-human species leads to antibodies produced by humans. Although these antibodies were “humanized”, the technology is limited because of the lack of antibody development and affinity maturation which naturally occurs in B cells. The specification further teaches that endogenous genes have been knocked out of mice and replaced with human counterparts to produce entirely human antibodies, but these mice have reduced

immune response. It is noted that the human antibodies produced by the transgenic mice have reduced affinity as compared to their mouse counterparts. See p. 42, lines 4-32. Thus, the instant specification teaches that the generation of chimeric antibodies, which utilize human variable regions, and mouse constant regions through B cell maturation can be used to produce high affinity human antibodies. See pp. 42-43, bridging ¶. The specification fails to provide teachings or guidance with regard to the generation of the claimed transgenic mice. Although the specification teaches production of mouse ES cells having a deletion of the OCR10 gene (Example 1), there is no guidance with regard to the generation of transgenic mice which would be able to produce chimeric or human antibodies. As noted by the specification, the production of such antibodies would require the correct rearrangement during the development of B cells. There is no evidence of record that shows that the claimed transgenic mice would be able to correctly produce chimeric or human antibodies as claimed, and as the specification and art support, such production would be considered unpredictable.

Accordingly, in view of the quantity of experimentation necessary for the use of ES cells from species other than mouse, the lack of direction or guidance, as well as the absence of working examples, provided by the specification for methods of genetically modifying ES cells from species other than mouse, as well as the unpredictable and undeveloped state of the art of ES cells, and the breadth of the claims encompassing any species of ES cells, the lack of teachings or guidance with

regard to the production of the claimed transgenic mice, and the claimed chimeric or human antibodies produced by said mice, it would have required undue experimentation for one skilled in the art to make and/or use the claimed genetically modified ES cells, and methods of using the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 51-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 51-53, 65-67, and 75 as written, are unclear. The claim recites a method of replacing an endogenous gene locus in eukaryotic cells. The claims read on methods of replacing gene loci both in vivo and in vitro. It is suggested that the claims be written to recite the term "isolated cell". Claims 54-64 depend from claim 53; claims 68-74 depend from claim 67, claims 76-78 depend from claim 75.

Claims 61, 72 and 77 are unclear. The claims do not recite that the ES cells is isolated. Thus, it is unclear if Applicants are attempting to claim an isolated ES cell, or a cell in an organism (which would encompass the entire organism). Appropriate correction is required.

Claims 59 and 73 written are unclear. The claims recite “a modified gene locus” and a “modified endogenous immunoglobulin variable region gene locus”. The claim is unclear because this can refer to a gene or a gene inside of an organisms. The recitation of the term “isolated” would be remedial. Clarification and/or amendment is requested.

Claims 62 and 78 are incomplete. The claims recite that the transgenic mouse is generated from an ES cell. An ES cell, by itself, cannot generate a transgenic mouse. For example, the ES cell must be introduced into a pseudopregnant or surrogate mother to develop to term to generate a transgenic mouse. Appropriate correction is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 51-55, 57-63, 65-69, 71-78 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuncherlapati *et al.* (WO 94/02602, 3 February 1994, Applicants' IDS filed 6/25/02).

Claims 59, 61, 72, 73, 77 are product by process claims. Where, as here, the claimed and prior art products are identical or substantially identical, or are

produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke*, *supra*. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

The claims are directed to genetically modified gene loci and to mouse ES cells comprising modified gene loci and methods of making the same.

Kuncherlapati *et al.* teach a method of using yeast artificial chromosomes [YACS] to produce mouse ES cells which have nonfunctional endogenous immunoglobulin genes, and have been introduced with xenogeneic, e.g., human heavy and light chain immunoglobulin genes [see p. 10, lines 27-37 and p. 11, lines 1-16]. Kuncherlapati *et al.* teach that the host immunoglobulin loci (both heavy

chain alleles and both light chain alleles (kappa and lambda)) would be rendered non-functional by homologous recombination by the introduction of homologous DNA via a construct that can disrupt or delete the target locus in embryonic stem cells. Further, Kuncherlapati *et al.* teach that in order to functionally inactivate each of the loci, there may be multiple transformations [see pp. 14-15, bridging paragraph]. Kuncherlapati *et al.* teach that in order to verify that homologous double crossover has occurred, negative selection (such as the Herpes simplex virus thymidine kinase gene) may be employed, furthermore to determine if homologous integration has occurred, DNA analysis by Southern blot hybridization can be used to establish the location of integration. Additionally, PCR may be used, wherein the PCR primers are complementary to a sequence within the targeting construct and complementary to a sequence and at the target locus to show that homologous recombination as occurred [see p. 17].

Accordingly, Kuncherlapati *et al.* anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 51-63, 65-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuncherlapati *et al.* (WO 94/02602, 3 February 1994, cited in Applicants' IDS) when taken with Yang *et al.* (*Nature Biotechnology*, 15: 859-865, 1997, from Applicants' Information Disclosure).

Kuncherlapati *et al.* teach a method of using yeast artificial chromosomes [YACs] to produce mouse ES cells which have nonfunctional endogenous immunoglobulin genes, and have been introduced with xenogeneic, e.g., human heavy and light chain immunoglobulin genes [see p. 10, lines 27-37 and p. 11, lines 1-16]. Kuncherlapati *et al.* teach that the host immunoglobulin loci (both heavy chain alleles and both light chain alleles (kappa and lambda)) would be rendered non-functional by homologous recombination by the introduction of homologous DNA via a construct that can disrupt or delete the target locus in embryonic stem

cells. Further, Kuncherlapati *et al.* teach that in order to functionally inactivate each of the loci, there may be multiple transformations [see pp. 14-15, bridging paragraph]. Kuncherlapati *et al.* teach that in order to verify that homologous double crossover has occurred, negative selection (such as the Herpes simplex virus thymidine kinase gene) may be employed, furthermore to determine if homologous integration has occurred, DNA analysis by Southern blot hybridization can be used to establish the location of integration. Additionally, PCR may be used, wherein the PCR primers are complementary to a sequence within the targeting construct and complementary to a sequence and at the target locus to show that homologous recombination as occurred [see p. 17].

Kuncherlapati *et al.* differ from the claimed invention in that they do not teach the use of bacterial homologous recombination to replace an endogenous immunoglobulin variable region gene locus with a homolgous or othologous human gene locus. However, prior to the time of the claimed invention, Yang *et al.* teach using bacterial artificial chromosomes [BACs] to generate transgenic mice expressing a lacZ transgene [see *Abstract* and page 863]. Particularly, Yang *et al.* teach using a BAC for targeted recombination [see Figure 1, p. 860]. Accordingly, in view of the combined teachings of Yang *et al.* and Kuncherlapati *et al.*, it would have been obvious to modify the method of using yeast artificial chromosomes [YACS] to produce mouse ES cells which have nonfunctional endogenous immunoglobulin genes, and have been introduced with xenogeneic, e.g., human

heavy and light chain immunoglobulin genes of Kuncherlapati *et al.* using BACs as described by Yang *et al.*, with a reasonable expectation of success. One of skill in the art would have been sufficiently motivated to make such a modification, as asserted by Yang *et al.* who state that using BAC systems to target homologous recombination overcomes various limitations of using YACs, such as, BAC libraries are easier to construct due to higher cloning efficiency, BACs have high stability and minimal chimerism, and BAC DNA is easy to isolate [see p. 859, 2nd column, 1st paragraph and p. 864, 1st paragraph].

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claim 51-55, 57-69, 71-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuncherlapati *et al.* (WO 94/02602, 3 February 1994) when taken with Lie *et al.* [Current Opinion Biotech, 1998, 9:43-48, cited on p. 7, Applicants' IDS, filed 6/25/02]. 64

Kuncherlapati *et al.* teach a method of using yeast artificial chromosomes [YACs] to produce mouse ES cells which have nonfunctional endogenous immunoglobulin genes, and have been introduced with xenogeneic, e.g., human heavy and light chain immunoglobulin genes [see p. 10, lines 27-37 and p. 11, lines 1-16]. Kuncherlapati *et al.* teach that the host immunoglobulin loci (both heavy

chain alleles and both light chain alleles (kappa and lambda)) would be rendered non-functional by homologous recombination by the introduction of homologous DNA via a construct that can disrupt or delete the target locus in embryonic stem cells. Further, Kuncherlapati *et al.* teach that in order to functionally inactivate each of the loci, there may be multiple transformations [see pp. 14-15, bridging paragraph]. Kuncherlapati *et al.* teach that in order to verify that homologous double crossover has occurred, negative selection (such as the Herpes simplex virus thymidine kinase gene) may be employed, furthermore to determine if homologous integration has occurred, DNA analysis by Southern blot hybridization can be used to establish the location of integration. Additionally, PCR may be used, wherein the PCR primers are complementary to a sequence within the targeting construct and complementary to a sequence and at the target locus to show that homologous recombination as occurred [see p. 17].

Kuncherlapati differ from the claimed invention in that they do not teach or suggest using quantitative PCR comprising TaqMan® technology or quantitative PCR using molecular beacons. However, prior to the time of the claimed invention, Lie *et al.* teach advances in PCR quantitation, using TaqMan [see p. 43, 1st column, last paragraph]. Lie *et al.* teach that TaqMan can be used to quantify the number of copies of a DNA template in a genomic DNA sample [see p. 46-47]. Accordingly, it would have been obvious for one of skill in the art to modify the method of using BACs to produce mouse ES cells which have nonfunctional endogenous

immunoglobulin genes, and have been introduced with xenogeneic, e.g., human heavy and light chain immunoglobulin genes as taught by Kuncherlapati *et al.* and Yang *et al.* by using a quantitative assay using TaqMan, as taught by Lie *et al.*, with a reasonable expectation of success. One of skill in the art would have been motivated to make such a modification, as there was an art-recognized need to improve quantitative PCR methods to evaluate factors such as gene copy numbers, mRNA expression, the efficiency of gene delivery systems, as asserted by Lie *et al.*, p. 43, 2nd paragraph.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

twt

Thaian N. Ton
Patent Examiner
Group 1632

Joe Wataad
AU1632